PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
LR/G-33815A/LEK		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/002107	28.02.2005	01.03.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4184 A61K31/695 A61K9/28 C07D403/10 C07C67/48

Applicant
LEK PHARMACEUTICALS D.D. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.12.2005	20.04.2006

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP2005/002107

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-10, 13-15, 18, 19	as originally filed
11, 12, 16, 17	received on 06.12.2005 with letter of 23.11.2005

Claims, Numbers

1-17	received on 06.12.2005 with letter of 23.11.2005

Drawings, Sheets

1/4-4/4	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 15-17

   because:

   ☒ the said international application, or the said claims Nos. 15-17 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 23.11.05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.
The amendments concerned are the following:
Claim 15: the last part of the claim (form D) which is based on page 2, first paragraph is there directed to the prior art and not to a form of the invention.
Claims 16 and 17: as they are now related to claim 15 which extends beyond the content of the application as filed, they also violate Art. 34 PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claim 17 is directed to a therapeutical method of treatment (Art. 34(4)(a)(I) and Rule 67.1 (iv) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: US-B1-6 740 775 (PFLAUM ZLATKO [SI]) 25 May 2004 (2004-05-25)
D2: WO 01/43723 A (BIOGAL GYOGYSZERGYAR RT; TEVA PHARMACEUTICALS USA, INC; KERI, VILMOS;) 21 June 2001 (2001-06-21)
D3: WO 03/048135 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; DOL) 12 June 2003 (2003-06-12)
D4: US-A-5 225 202 (HODGES ET AL) 6 July 1993 (1993-07-06)
D5: WO 01/93859 A (LEK PHARMACEUTICAL AND CHEMICAL COMPANY D.D; PFLAUM, ZLATKO; MILIVOJEV) 13 December 2001 (2001-12-13)
D6: US-A-5 140 037 (CHIU ET AL) 18 August 1992 (1992-08-18)

Novelty:
The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-13 is new in the sense of Article 33(2) PCT.
A process for the preparation of a composition comprising a step of wet granulation where

both ratios of active and microcrystalline cellulose and/or active and granulating liquid are defined to be above as in claim is not disclosed in any one cited prior art.

A composition comprising pravastatin sodium which exhibits X-Ray diffraction pattern below 2° as defined in claim 14 is disclosed in D1 or D2. The subject-matter of said claim does not contain further technical features which might make a difference to the compositions of D1 or D2.
Thus, the subject-matter of claim 14 is not new.

Inventive step:
The problem of stabilizing a composition of an active which exists in a polymorph form susceptible to degradation or interconversion into other polymer forms has been presently solved by a specific wet granulation process in which an alcoholic liquid (granulating liquid) has been used (see in particular p. 2 and 3 in the description).
However, this fact which is necessary to solve the posed problem has not been reflected in the wording of claims 1-14. According to the wording of claim 1 any kind of a granulating liquid be useful, where no evidence for that can be found in the application. These above concerns are also not considered in the subject-matter of claim 14.
Accordingly, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1-14 does not involve an inventive step in the sense of Article 33(3) PCT.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
US-B1-6 740 775	25.05.04	04.04.03	

Re Item VIII
Certain observations on the international application
-Claim 9 is not allowable (Rule 6.2(a) PCT and Guidelines CIII, 4.10) due to the wording "substantially similar to that in FIG.1".

Example 3

14.8 g of pravastatin sodium is added to a vessel and while mixing 9 g of a 6.3 % solution of water in ethanol is sprayed onto the sample. The granules thus formed are dried under vacuum at 50 °C for 12 hours. The dry sample is analyzed with XRPD. The sample contains crystalline pravastatin sodium form LEK.

Example 4

9.9 g of pravastatin sodium is added to a vessel and while mixing 9 g of a solution of PVP K25 (20 %) and water (4.4 %) in ethanol is sprayed onto the sample. The granules thus formed are dried under vacuum at 50 °C for 12 hours. The dry sample is analyzed with XRPD. The sample contains crystalline pravastatin sodium form LEK.

The results of Examples 1-4 are summarized in Table I

Table 1 Polymorph analysis results after granulation of crystalline pravastatin sodium form LEK with ethanol and ethanol solution of PVP

Example No.	Experiment conditions	XRPD results	DSC results
1	15 g pravastatin Na + 15 g ethanol, drying in vacuum at RT, 12 h	**form LEK**	form LEK
2	12.4 g pravastatin Na + 12 g of 20 % PVP solution in ethanol, drying in vacuum at RT, 12 h	**form LEK + form D**	-
3	14.8 g pravastatin Na + 9 g of ethanol containing 6,3 % water, drying in vacuum at 50 °C, 12 h	**form LEK**	-
4	9.9 g pravastatin Na + 9 g of 20 % PVP solution in wet ethanol (4.4 % water), drying in vacuum at 50 °C, 12 h	**form LEK**	-

These Examples demonstrate that use of alcohol as a granulating liquid, for example absolute ethanol or aqueous ethanol, does not cause the precrystallization (conversion into another polymorph form) of pravastatin sodium in the absence of other ingredients. However, granulation with a granulating liquid comprising a binder (PVP) does in some experiments induce a partial conversion as summarized in Table 1.

The following Examples demonstrate the influence of granulating liquid (ethanol, water) optionally comprising polyvinylpyrrolidone on the one hand, and the influence of additional excipients in certain weight ratios on the other hand (microcrystalline cellulose, lactose, anhydrous disodium hydrogenphosphate, crosslinked carboxymethylcellulose sodium and sodium lauryl sulfate) on the interconversion of an active pharmaceutical ingredient which exists in a first polymorph into one or more other polymorph forms.

Avicel™, Vivapur™ and Microcel™ are commercially available forms of microcrystalline cellulose.

Example 5

3 g of pravastatin sodium and 12.6 g of Avicel PH 112 are added to a vessel and while mixing 10 g of ethanol is sprayed onto the sample. A portion of the granules thus formed are

Table 2: Polymorph analysis results of granulation of crystalline pravastatin sodium form LEK together with excipients using ethanol as a granulating liquid

Example No.	Experiment conditions	XRPD results
5	12.6 g **Avicel** + 3 g pravastatin Na + 10 g ethanol, drying in vacuum at RT and 50 °C	**form D**
6	12 g **dried Avicel** + 3 g pravastatin Na + 10 g ethanol, drying in vacuum at RT and 50 °C	**form D**
7	3 g **lactose** + 6 g pravastatin Na + 9 g ethanol, drying in vacuum at 50 °C	**form LEK**
8	6 g **Na_2HPO_4** + 5 g pravastatin Na + 9 g ethanol, drying in vacuum at 50 °C	**form LEK**
9	2 g **Ac-Di-Sol** + 10 g pravastatin Na + 11 g ethanol, drying in vacuum at 50 °C	**form LEK**
10	1 g **Texapon** + 10 g pravastatin Na + 11 g ethanol, drying in vacuum at 50 °C	**form LEK**
11	2 g **Avicel** + 4 g pravastatin Na + 9 g ethanol, drying in vacuum at 50 °C	**form LEK + form D**

12	2 g **Avicel** + 4 g pravastatin Na + 3 g ethanol, drying in vacuum at 50 °C	**form LEK**
13	6 g **Avicel** + 6 g pravastatin Na + 3 g ethanol, drying in vacuum at RT	**form LEK**
14	6 g **Vivapur** + 6 g pravastatin Na + 3 g ethanol, drying in vacuum at RT	**form LEK**
15	6 g **Microcel** + 6 g pravastatin Na + 3 g ethanol, drying in vacuum at RT	**form LEK**
16	6 g **Avicel** + 6 g pravastatin Na + 7 g ethanol, drying in vacuum at RT	**form LEK + form D**
17	0.5 g **Avicel** + 0.5 g pravastatin Na, dry mixture, 2 h on 60 °C	**form LEK**

These Examples show that conversion of the polymorph form is detected when microcrystalline cellulose such as Avicel™, Vivapur™ or Microcel™ is used at certain ratios to active pharmaceutical ingredient, and this phenomenon is also dependent on the amount of granulating liquid used.

One can conclude that pravastatin sodium precrystallizes to form D in the presence of a high amount of microcrystalline cellulose and granulating liquid. Pravastatin sodium in the Lek form is, however, stable if the mass ratio of pravastatin sodium to microcrystalline cellulose is

Claims

1. A process for the preparation of a pharmaceutical composition comprising an active pharmaceutical ingredient capable of existing in multiple polymorphic forms, comprising a step of wet granulation of granulate comprising said active pharmaceutical ingredient and microcrystalline cellulose and liquid, wherein in said wet granulate the weight ratio of active pharmaceutical ingredient to microcrystalline cellulose is above 1.0 and/or the weight ratio of active pharmaceutical ingredient to granulating liquid is above 1.0.

2. A process according to claim 1 wherein said wet granulate is an alcoholic phase and in said wet granulate the weight ratio of active pharmaceutical ingredient to microcrystalline cellulose is above 1.0 and the weight ratio of active pharmaceutical ingredient to alcoholic liquid is above 1.0.

3. A process according to claim 1 or claim 2 wherein said weight ratio of active pharmaceutical ingredient to the liquid is above 2.0.

4. A process according to any preceding claim wherein said liquid is an alcoholic liquid consisting only absolute ethanol or of an aqueous ethanol solution.

5. A process according to any preceding claim wherein said microcrystalline cellulose is incorporated into the composition in more than one step.

6. A process according to any preceding claim wherein the active pharmaceutical ingredient is pravastatin sodium.

7. A process according to claim 6 wherein the liquid is ethanol and the weight ratio of pravastatin sodium to microcrystalline cellulose is above 1.0 and the weight ratio of pravastatin sodium to ethanol is above 2.0.

8. A process according to any preceding claim wherein the active pharmaceutical ingredient is crystalline pravastatin sodium having characteristic peaks in a X-ray diffractogram at 2θ of 4, 10,2, 16,3, 17,3, and 20,0 ± 0,2°.

9. A process according to claim 8 wherein the crystalline pravastatin sodium exhibits an X-ray diffraction pattern substantially similar to that in FIG 1.

10. A process according to any of claims 6 to 9 whereby pravastatin sodium in a first polymorph form is stabilized against conversion into a polymorph form which exhibits broad peaks in X-ray diffraction pattern, having half-value widths of significant peaks above 2° 2 Theta.

11. A process according to any preceding claim wherein a binder is incorporated into the composition in a step other than the step of preparation of an alcoholic phase.

12. A process according to claim 11 wherein said binder is polyvinylpyrrolidone (PVP).

13. A pharmaceutical composition obtained by the process of any preceding claim.

14. A stabilized pharmaceutical composition comprising the polymorph form of pravastatin sodium which exhibits X-Ray diffraction pattern with significant peaks having half-value widths below 2° 2 Theta characterized in that the polymorph form of pravastatin sodium is stabilized against converting into one exhibiting peaks in X-ray diffraction pattern, having half-value widths of significant peaks above 2° 2 Theta.

15. A stabilized pharmaceutical composition comprising the polymorph form of pravastatin sodium which exhibits X-Ray diffraction pattern with significant peaks at 4, 10,2, 16,3, 17,3, and 20,0 ± 0,2° 2 Theta characterized in that no conversion occurs to polymorph form which is characterized by three broad peaks between about 2° and 12° 2 Theta and one very broad peak extending from about 15° to 25° 2 Theta in its X-ray powder diffraction pattern.

16. Use of a pharmaceutical composition according to of any of the claims 13 to 15 for the manufacture of a medicament for treatment of hypercholesterolemia.

17. A method of preventing or treating hypercholesterolemia in a susceptible patient, comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any of the claims 13 to 15.